

IN THE SPECIFICATION:

Please replace the following paragraphs:

[0029] Furthermore, the present invention provides host cells harboring transfected CPKGs. These cells can be used for the treatment of cancers. The present invention also provides knock-out animals in which the genomic ~~sequence~~sequence of at least one CPKG is disrupted.

[0077] In many other embodiments, the cancer genes of the present invention include "cancer-related protein kinase gene (CPKG)." CPKGs are protein kinase genes that are identified by the two-tier statistical analysis of the Gene LogicGene Logic® BioExpress® database as showing higher levels of mRNA expression in tumor specimens when compared with the corresponding cancer-free (normal) tissue samples. Examples of the CPKGs of the present invention are shown in Table 1. The mRNA molecules of these CPKGs were found to be up-regulated in tissues from at least two of the four major types of cancers, i.e., colon adenocarcinoma, lung adenocarcinoma, breast infiltrating ductal carcinoma, and prostate adenocarcinoma. The kinases encoded by the CPKGs are referred to as cancer-related protein kinases (CPKs).

[0096] ERBB2/HER2/NEU (v-erb-b2 erythroblastic leukemia viral oncogene homolog 2, neuro/glioblastoma derived oncogene homolog (avian)): ERBB2 is a tyrosine kinase receptor and a component of IL-6 signaling through the MAP kinase pathway. ERBB2 is similar to the EGF receptor. Overexpression of ERBB2 confers ~~Taxol~~Taxol® resistance in breast cancer cells. Transfected MDA-MB-435 cells that overexpress HER2 transcriptionally upregulates CDKN1A which when associated with CDC2 would inhibit ~~Taxol~~Taxol®-mediated CDC2 activation, and delay cell entrance to G.sub.2/M phase, and thereby inhibits ~~Taxol~~Taxol®-induced apoptosis. In CDKN1A anti sense-transfected MDA-MB-435 cells or in p21/MEF cells, ERBB2 was unable to inhibit ~~Taxol~~Taxol®-induced apoptosis. Therefore, CDKN1A participates in the regulation of a G.sub.2/M checkpoint that contributes to resistance to ~~Taxol~~Taxol®-induced apoptosis in ERBB2-over-expressing breast cancer cells. The TMHMM profile of ERBB2 is shown in FIG. 18.

[0120] STK39/SPAK/Ste-20 related kinase: Human STK39 is very similar to rat SPAK. SPAK modulates p38 MAP kinase activity and exhibits increased expression in androgen-treated LNCaP cells. R1881-induced SPAK expression was completely

abrogated by the antiandrogen ~~casodex~~casodex® and by actinomycin D indicating that androgen induction of SPAK requires the androgen receptor and transcription. Cycloheximide caused a partial inhibition of R1881-induced SPAK expression which suggests that androgen induction of SPAK expression may require synthesis of additional proteins. Northern blot and ribonuclease protection assays demonstrated that SPAK is expressed at high levels in normal human testes and prostate, as well as in a number of breast and prostate cancer cell lines. The TMHMM profile of STK39 is shown in FIG. 43.

[0141] Purines and purine analogs act as CDK inhibitors. Flavopiridol (L86-2,275) is a flavonoid that causes 50% growth inhibition of tumor cells at 60 nM (57). It also inhibits EGFR and protein kinase A. Flavopiridol~~Flavopiridel~~ induces apoptosis and inhibits lymphoid, myeloid, colon, and prostate cancer cells grown in vivo as tumor xenografts in nude mice.

[0146] The most successful strategy to selectively kill tumor cells is the use of monoclonal antibodies (mAbs) that are directed against the extracellular domain of RTKs which are critically involved in cancer and are expressed at the surface of tumor cells. In the past years, recombinant antibody technology has made enormous progress in the design, selection and production of new engineered antibodies, and it is possible to generate humanized antibodies, human-mouse chimeric or biospecific antibodies for targeted cancer therapy. Mechanistically, anti-RTK mAbs might work by blocking the ligand-receptor interaction and therefore inhibiting ligand-induced RTK signaling. In addition, by binding of to certain epitopes on the cancer cells, the anti-RTK mAbs induce immune-mediated responses such as opsonization and complement-mediated lysis and trigger antibody-dependent cellular cytotoxicity by macrophages or natural killer cells. In recent years, it became evident that mAbs control tumor growth by altering the intracellular signaling pattern inside the targeted tumor cell, leading to growth inhibition and/or apoptosis. In contrast, biospecific antibodies can bridge selected surface molecules on a target cell with receptors on an effector cell triggering cytotoxic responses against the target cell. Despite the toxicity that has been seen in clinical trials of bispecific antibodies, advances in antibody engineering, characterization of tumor antigens and immunology might help to produce rationally designed bispecific antibodies for anti-cancer therapy.

[0157] ~~ressa~~ressa® (ZD1839) is an orally active selective EGF-R inhibitor.

This compound disrupts signaling involved in cancer cell proliferation, cell survival and tumor growth support by the host. The clinical efficacy of this agent shows that it is well tolerated by patients undergoing Phase I/II clinical trials. The compound has shown promising cytotoxicity towards several cancer cell lines.

Please replace Table 2, at page 30, of the specification as filed, with the enclosed table:

TABLE 2. RTK Drugs Currently Under Clinical Evaluation

RTK	Drug	Company	Description	Status
EGFR	ZA18539 ressa <u>ressa</u> ®	AstraZeneca	TKI that inhibits EGFR signaling	Phase III
EGFR	Cetuximab C225	ImClone Systems	Mab directed against EGFR	Phase III
EGFR	EGF fusion protein	Seragen	Recombinant diphtheria toxin-hEGF fusion protein	Phase II
HER2	Trastuzumab Hereceptin <u>Herceptin</u> ®	Genetech	Mab directed against HER2	Approved by the FDA in 1998
IGF-IR	INX-4437	INEX USA	Antisense oligonucleotides targeting IGR-IR	Phase I
VEGFR	SU5416	SUGEN	TKI that inhibits VEGFR2	Phase II
VEGFR/ FGFR/ FGFR	SU6668	SUGEN	RTK inhibition of VEGFR and PDGFR PDGFR	Phase I